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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/783,128	MCSWIGGEN, JAMES	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,13-21 and 30-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,13-21 and 30-32* is/are rejected.

7)☒ Claim(s) *18* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/20/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/03/2006 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed 10/03/2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 04/03/2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 04/03/2006, claims 1, 3, 13-21 and 30-32 are pending in the application. Applicant has canceled claims 2, 4-12 and 22-29.

Priority

Applicant does not receive the benefit of the earlier filed applications because the prior applications do not provide adequate support for the claims of the instant application and thus applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120.

The instant application does not receive the benefit of any of the earlier filed priority documents because the instantly cited invention of a siNA molecule targeted to a human huntingtin (HD) nucleotide sequence wherein about 100% of nucleotide positions in one or both strands of said siNA molecule are chemically modified, is not supported by the specification or claims of the priority applications. In the Remarks filed 01/10/2006, Applicant points to support in the provisional application 60/363,124 for the instantly cited siNA targeted to a HD nucleotide sequence. The provisional application 60/363,124 does disclose a siNA targeted to a HD nucleotide sequence, however, the limitation wherein "about 100% of nucleotides positions in one or both strands of said siNA molecule are chemically modified" are not supported by the specification of application 60/363,124. If Applicant believes the prior application provides support then applicant must point, with particularity, to where such support can be found in the specification of the prior application.

Thus, the claims are accorded a priority date of 02/20/2004, the filing date of the instant application.

Information Disclosure Statement

The submission of the Information Disclosure Statement on 03/20/2006 is in compliance with 37 CFR 19.7. The information disclosure statement has been considered by the examiner and signed copies have been placed in the file.

Specification

The disclosure is objected to because of the following informalities: The disclosure appears to be missing pages 49-69. Appropriate correction is required.

Claim Objections

Claim 18 is objected to because of the following informalities: Claim 18 does not have a period at the end of the sentence. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 13-21 and 30-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 13-21 and 30-31 of copending Application No. 10/824,036, in view of Rana, T. (US 2005/0020521).

This is a provisional obviousness-type double patenting rejection.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

The instant claims are drawn to a chemically modified double stranded short interfering nucleic acid (siNA) molecule comprising a distinct sense strand and an antisense strand wherein each strand of said siNA is about 18 to about 27 nucleotides in length and the antisense strand comprises a nucleotide sequence of about 18 to about 27 nucleotides that is complementary to a human HD nucleotide sequence and about 100% of nucleotide positions in one or both strands of said siNA molecule are chemically modified. The instant claims are further drawn to such siNA molecule wherein the siNA molecule comprises one or more ribonucleotides, wherein one or more pyrimidine nucleotides in the sense or antisense strand are 2'-O-methyl or 2'-O-deoxy-2'-fluoro, wherein one or more purine nucleotides in the sense or antisense strand are 2'-deoxy or 2'-O-methyl, wherein the sense strand comprises a terminal cap moiety at the 5'-end, the 3'-end or both, wherein the antisense strand comprises a terminal phosphorothioate internucleotide linkage, wherein the 5' end includes a terminal 5'-phosphate and further drawn to a pharmaceutical composition comprising said siNA.

Claims 1, 3, 13-21 and 30-32 of copending Application 10/824,036 are drawn to a siRNA molecule wherein each strand of said siNA is about 18 to about 27 nucleotides in length and wherein one strand is complementary to a human HD nucleotide sequence and wherein one or more pyrimidine nucleotides present in one or both strands of said siRNA molecule is a 2'-deoxy-2'-fluoro pyrimidine modification. The claims of copending Application 10/824,036 are further drawn to such siRNA molecule wherein the double stranded nucleic acid molecule comprises one or more ribonucleotides, wherein one or more pyrimidine nucleotides in the sense or antisense strand are 2'-O-methyl or 2'-O-deoxy-2'-fluoro, wherein one or more purine nucleotides in the sense or antisense strand are 2'-deoxy or 2'-O-methyl, wherein the sense strand comprises a terminal cap moiety at the 5'-end, the 3'-end or both, wherein the antisense strand comprises a terminal phosphorothioate internucleotide linkage, wherein the 5' end includes a terminal 5'-phosphate and further drawn to a pharmaceutical composition comprising said double stranded nucleic acid.

The claims of copending application 10/824,036 fail to disclose such siRNA wherein about 100% of nucleotide positions in one or both strands of said siRNA molecule are chemically modified. Rana teach that such siRNA can be modified at internal residues such that properties like increased chemical stability and nuclease resistance are improved without compromising the RNA interference activity (see paragraph 0029). Rana teach that the RNAi mechanism does not require 2'-OH chemical groups and these groups could be replaced with such nucleotides such as 2'-deoxy, 2'-O methyl and 2'-fluoro and the will still efficiently induce RNAi in human cells.

Rana teach the siRNA can comprise one or more chemical modifications in the sugar or nucleobase groups and teach the siRNA can comprise any combination of two or more modifications (see paragraphs 0036-0040). Rana teach that sense and/or antisense strands of such siRNA can comprise 100% of chemically modified nucleotides and specifically teach such siRNA comprising 100% of chemically modified nucleotides are stable (see Figure 12).

Therefore, it would have been obvious to make a siRNA molecule comprising chemical modifications in all nucleotides in one or both strands One of ordinary skill would have been motivated to incorporate chemical modifications in all nucleotides in one or both strands because Rana teach that such siRNA comprising chemical modifications enhance the molecules chemical stability and nuclease resistance and further such modifications are important for in vivo applications, particularly human therapeutics.

New Claim Rejections - 35 USC § 103

Applicant's arguments filed 10/03/2006 regarding the rejection of record under 35 U.S.C. 103(a) that are considered relevant to the instant claims and newly applied rejection under 35 U.S.C. 103(a) will be discussed below.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 13-15, 18-21 and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayden et al. (recited on PTO form 892 filed 08/10/2005), Rana (US 2005/0020521), Hammond et al. (recited on PTO form 892 filed 08/10/2005) and Vickers et al. (J. Biological Chemistry 2003) Bass et al (Nature, 2001) and evidenced by Caplen (Expert Opin Biol Ther, 2003 July).

The instant claims are drawn to a chemically modified double stranded short interfering nucleic acid (siNA) molecule comprising a distinct sense strand and an antisense strand wherein each strand of said siNA is about 18 to about 27 nucleotides in length and the antisense strand comprises a nucleotide sequence of about 18 to about 27 nucleotides that is complementary to a human HD nucleotide sequence and about 100% of nucleotide positions in one or both strands of said siNA molecule are chemically modified. The instant claims are further drawn to such siNA molecule wherein the siNA molecule comprises one or more ribonucleotides, wherein one or more pyrimidine nucleotides in the sense or antisense strand are 2'-O-methyl or 2'-O-deoxy-2'-fluoro, wherein one or more purine nucleotides in the sense or antisense strand are 2'-deoxy or 2'-O-methyl, wherein the sense strand comprises a terminal cap moiety at the 5'-end, the 3'-end or both, wherein the antisense strand comprises a terminal phosphorothioate internucleotide linkage, wherein the 5' end includes a terminal 5'-phosphate and further drawn to a pharmaceutical composition comprising said double stranded nucleic acid.

Hayden et al. teach an antisense compound targeted to a HD gene (see paragraph 0082). Hayden et al. teach Huntingtin's Disease is a neurodegenerative disease caused by a mutation in the huntingtin protein that leads to neuronal cell death and further teach inhibition of a gene encoding a huntingtin protein leads to inhibition of apoptosis of neuronal cells. Hayden et al. further teach the antisense compound can comprise sugar, nucleobase and internucleoside modifications to increase the biological stability of said compound and enhance cellular uptake and further increase the antisense compounds affinity for the target sequence. (see paragraph 0087). Hayden et al. do not teach a double-stranded nucleic acid molecule targeted to a HD gene and further do not teach the nucleotides of the sense and antisense strands comprise chemical modifications.

Hammond et al. teach two methods for silencing specific genes: antisense and RNA interference. Hammond et al. teach that although antisense methods are straightforward techniques for probing gene function, the methods have suffered from "...questionable specificity and incomplete efficacy." (see page 110, column 1). Hammond et al. further teach " "...dsRNAs have been shown to inhibit gene expression in a sequence-specific manner" and further "RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression." Likewise, Vickers et al. teach that RNA interference using siRNA oligonucleotides has become "a powerful and widely used tool for the analysis of gene function..." and that siRNA has proven to be more potent and effective than traditional antisense approaches. Similarly, Bass et al. states that RNA interference using siRNA has "...repeatedly proven itself to be more robust

than antisense techniques: It works more often, and typically decreases expression of a gene to lower levels, or eliminates it entirely." Bass et al. points out that siRNAs are effective at targeting transgenes as well as naturally occurring endogenous genes (see page 428). Bass et al. further states "...siRNAs are effective at concentrations that are several orders of magnitude below the concentrations typically used in antisense experiments."

Rana teach siRNA molecules which are 10-50 nucleotides in length and preferably 18-25 nucleotides in length that are capable of directing or mediating RNA interference (see paragraph 0070). Rana teach such siRNA molecules are comprised of separate sense and antisense strands wherein the siRNA comprises a sequence that is complementary to a target mRNA to direct target specific RNA interference. Rana further teach the siRNA comprises a 5' phosphate group attached to the hydroxyl group of the 5' sugar (see paragraph 0059). Rana teach that such siRNA can be modified at internal residues such that properties such as chemical stability and nuclease resistance are improved without compromising the RNA interference activity (see paragraph 0029). Rana teach that the RNAi mechanism does not require 2'-OH chemical groups and these groups could be replaced with such nucleotides such as 2'-deoxy, 2'-O methyl and 2'-fluoro and the siRNA was still able to efficiently induce RNAi in human cells. Rana teach the 3' terminal end or the 5' terminal end of the siRNA can be modified with such groups as peptides, cross linkers or organic compounds (see paragraph 0033). Rana teach pharmaceutical compositions comprising such siRNA (see paragraph 207). Rana teach the siRNA can comprise one or more chemical

modifications in the sugar or nucleobase groups and teach the siRNA can comprise any combination of two or more modifications (see paragraphs 0036-0040). Rana teach that sense and/or antisense strands of such siRNA can comprise at least 100% of chemically modified nucleotides and specifically teach such siRNA comprising 100% of chemically modified nucleotides are stable (see Figure 12).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a siRNA molecule, as taught by Hammond et al., Vickers et al. and Rana to target a gene encoding HD, as taught by Hayden et al. Further it would have been obvious for one of ordinary skill in the art to make siRNA nucleic acid molecules with chemical modifications in the sense or antisense strand, as taught by Rana.

One would have been motivated to use a siRNA targeted to a HD gene and inhibit gene expression because Hayden et al. teach HD proteins are involved in neurodegenerative diseases and inhibition of HD expression inhibits apoptosis of neuronal cells (see paragraph 0007). One would have been motivated to use a siRNA targeted to HD instead of an antisense because it was well known at the time the invention was made that dsRNA molecules are efficient molecules to target and decrease expression of a target gene given that Hammond et al. teach using dsRNA to inhibit gene expression is more sequence specific than using antisense methodologies and RNAi using dsRNA is a more potent method requiring only a few molecules of dsRNA per cell and given that Vickers et al. teach siRNA are more potent than antisense compounds. Further, because Rana teach the RNAi mechanism does not

require 2'-OH chemical groups, one of skill in the art would have been motivated to incorporate 2'-O-methyl, 2'-deoxy or 2'-deoxy-2'-fluoro chemical modifications in one or both strands as specifically taught by Rana to increase the duplex stability. One would therefore be motivated to chemically enhance the siRNAs resistance to nucleases while preserving or maximizing its activity in order to most effectively target the desired gene. The motivation to chemically modify siRNA is further evidenced by Caplen (Expert Opin Biol Ther, 2003 Jul, 3(4), pp. 575-86), who points out that, "Many of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system..." (see page 581). As evidenced by Caplen, RNA interference encounters similar problems as other nucleic acid based therapies and therefore, one would be motivated to incorporate each of the above-mentioned modifications in an attempt to enhance delivery of any of the sequence specific oligonucleotide therapeutics.

Finally, one would have a reasonable expectation of success because Hayden et al. teach antisense molecules can be targeted to a HD gene and regulate gene expression, Hammond et al. and Vickers et al. teach that of the two methods used for silencing gene function, RNAi using dsRNA is more potent and sequence specific than antisense. One would have had a reasonable expectation of success at introducing chemical modifications wherein about 100% of the nucleotides were modified given that Rana specifically teach such siRNA are more stable and such siRNA are capable of

eliciting RNA interference activity in cells. Further, one would have a reasonable expectation of success because chemical modifications of an oligonucleotide, adding stability and specificity to oligonucleotides were known in the art at the time of the invention was made. Additionally, one would expect such modifications would benefit siRNAs because such modifications had been shown to benefit antisense or ribozymes.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention.

Claims 1, 3, 13-21 and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayden et al. (recited on PTO form 892 filed 08/10/2005), Rana, T. (US 2005/0020521), Hammond et al. (recited on PTO form 892 filed 08/10/2005) and Vickers et al. (J. Biological Chemistry 2003) and evidenced by Caplen (Expert Opin Biol Ther, 2003 July) and in further view of Matulic-Adamic (recited on PTO form 892 filed 08/10/2005).

The instant claims are drawn to a chemically modified double stranded short interfering nucleic acid (siNA) molecule comprising a distinct sense strand and an antisense strand wherein each strand of said siNA is about 18 to about 27 nucleotides in length and the antisense strand comprises a nucleotide sequence of about 18 to about 27 nucleotides that is complementary to a human HD nucleotide sequence and about 100% of nucleotide positions in one or both strands of said siNA molecule are chemically modified. The instant claims are further drawn to such siNA molecule wherein the double stranded nucleic acid molecule comprises one or more

ribonucleotides, wherein one or more pyrimidine nucleotides in the sense or antisense strand are 2'-O-methyl or 2'-O-deoxy-2'-fluoro, wherein one or more purine nucleotides in the sense or antisense strand are 2'-deoxy or 2'-O-methyl, wherein the sense strand comprises a terminal cap moiety at the 5'-end, the 3'-end or both, wherein the terminal cap moiety is an inverted deoxy abasic moiety, wherein the antisense strand comprises a terminal phosphorothioate internucleotide linkage, wherein the 5' end includes a terminal 5'-phosphate and further drawn to a pharmaceutical composition comprising said double stranded nucleic acid.

Hayden et al., Rana, T., Hammond et al., Vickers et al. and Caplen et al. are relied upon for the reasons set forth above. Hayden et al., Rana, T., Hammond et al., Vickers et al. and Caplen et al. do not teach siRNA comprising wherein the sense strand comprises a terminal cap moiety at the 5'-end, the 3'-end or both, wherein the terminal cap moiety is an inverted deoxy abasic moiety.

Matulic-Adamic et al. teach double stranded structures comprising abasic terminal cap moieties that provide resistance to degradation (see column 2, lines 44-55 and column 3 lines 1-68).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a siRNA molecule, as taught by Hammond et al. and Vickers et al. and Rana T. to target a gene encoding HD, as taught by Hayden et al. Further it would have been obvious for one of ordinary skill in the art to make a double siRNA molecules with chemical modifications, as taught by Rana and Matulic-Adamic et al. Matulic-Adamic et al. provide motivation to make a siRNA with terminal cap moieties

to provide resistance and degradation given that Matulic-Adamic et al. teach double stranded structures comprising terminal cap moieties.

Finally, one would have a reasonable expectation of success because Hayden et al. teach antisense molecules can be targeted to a HD gene and regulate gene expression, Hammond et al. and Vickers et al. teach that of the two methods used for silencing gene function, RNAi using dsRNA is more potent and sequence specific than antisense and finally Rana teach designing siRNA with chemical modifications that mediate RNA interference. Further, one would have a reasonable expectation of success because chemical modifications of an oligonucleotide, adding stability and specificity to oligonucleotides were known in the art at the time of the invention was made. Additionally, one would have expected such modifications would benefit siRNAs because such modifications had been shown to benefit antisense or ribozymes.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention.

Claims 1, 3, 13-21 and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davidson et al. (US 2004/0241854), Rana (US 2005/0020521), Matulic-Adamic (recited on PTO form 892 filed 08/10/2005) and evidenced by Caplen (Expert Opin Biol Ther, 2003 July).

The instant claims are drawn to a chemically modified double stranded short interfering nucleic acid (siNA) molecule comprising a distinct sense strand and an antisense strand wherein each strand of said siNA is about 18 to about 27 nucleotides

in length and the antisense strand comprises a nucleotide sequence of about 18 to about 27 nucleotides that is complementary to a human HD nucleotide sequence and about 100% of nucleotide positions in one or both strands of said siNA molecule are chemically modified. The instant claims are further drawn to such siNA molecule wherein the double stranded nucleic acid molecule comprises one or more ribonucleotides, wherein one or more pyrimidine nucleotides in the sense or antisense strand are 2'-O-methyl or 2'-O-deoxy-2'-fluoro, wherein one or more purine nucleotides in the sense or antisense strand are 2'-deoxy or 2'-O-methyl, wherein the sense strand comprises a terminal cap moiety at the 5'-end, the 3'-end or both, wherein the terminal cap moiety is an inverted deoxy abasic moiety, wherein the antisense strand comprises a terminal phosphorothioate internucleotide linkage, wherein the 5' end includes a terminal 5'-phosphate and further drawn to a pharmaceutical composition comprising said double stranded nucleic acid.

Davidson et al. teach siRNA directed to a HD nucleotides sequence. Davidson et al. teach siRNA are ideal compounds to target mutant alleles such as found in HD (see paragraphs 0043 and 0052). Davidson et al. teach such siRNA are less than 30 nucleotides and preferably 19 to 25 nucleotides in length and comprise two strands (see paragraph 0144). Davidson et al. specifically teach such siRNA inhibition of the expression of a huntingtin protein (see Example 4 and Figure 15). Davidson et al. does not teach such siRNA comprising chemical modifications of the sense or antisense strand wherein about 100% of nucleotide positions in one or both strands of said siNA molecule are chemically modified.

Rana teach siRNA molecules which are 10-50 nucleotides in length and preferably 18-25 nucleotides in length that are capable of directing or mediating RNA interference (see paragraph 0070). Rana teach such siRNA molecules are comprised of separate sense and antisense strands wherein the siRNA comprises a sequence that is complementary to a target mRNA to direct target specific RNA interference. Rana further teach the siRNA comprises a 5' phosphate group attached to the hydroxyl group of the 5' sugar (see paragraph 0059). Rana teach that such siRNA can be modified at internal residues such that properties such as chemical stability and nuclease resistance are improved without compromising the RNA interference activity (see paragraph 0029). Rana teach that the RNAi mechanism does not require 2'-OH chemical groups and these groups could be replaced with such nucleotides such as 2'-deoxy, 2'-O methyl and 2'-fluoro and phosphorothioate and the siRNA was still able to efficiently induce RNAi in human cells. One would therefore be motivated to chemically enhance the siRNAs resistance to nucleases while preserving or maximizing its activity in order to most effectively target the desired gene Rana teach the 3' terminal end or the 5' terminal end of the siRNA can be modified with such groups as peptides, cross linkers or organic compounds (see paragraph 0033). Rana teach pharmaceutical compositions comprising such siRNA (see paragraph 207). Rana teach the siRNA can comprise one or more chemical modifications in the sugar or nucleobase groups and teach the siRNA can comprise any combination of two or more modifications (see paragraphs 0036-0040). Rana teach that sense and/or antisense strands of such siRNA can comprise at least 100% of chemically modified nucleotides and specifically

teach such siRNA comprising 100% of chemically modified nucleotides are stable (see Figure 12).

Matulic-Adamic et al. teach double stranded structures comprising abasic terminal cap moieties that provide resistance to degradation (see column 2, lines 44-55 and column 3 lines 1-68).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate such chemical modifications as taught by Rana into the siRNA targeted to a HD nucleotide sequence, as taught by Davidson et al. Matulic-Adamic et al. provide motivation to make a siRNA with terminal cap moieties to provide resistance and degradation given that Matulic-Adamic et al. teach double stranded structures comprising terminal cap moieties and incorporate of such modifications increases the molecules stability and nuclease resistance.

One would have been motivated to incorporate chemical modifications because Rana teach the RNAi mechanism does not require 2'-OH chemical groups, one of skill in the art would have been motivated to incorporate 2'-O-methyl, 2'-deoxy or 2'-deoxy-2'-fluoro chemical modifications in one or both strands as specifically taught by Rana to increase the duplex stability. The motivation to chemically modify siRNA is further evidenced by Caplen (Expert Opin Biol Ther, 2003 Jul, 3(4), pp. 575-86), who points out that, "Many of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system..."

(see page 581). As evidenced by Caplen, RNA interference encounters similar problems as other nucleic acid based therapies and therefore, one would be motivated to incorporate each of the above-mentioned modifications in an attempt to enhance delivery of any of the sequence specific oligonucleotide therapeutics.

Finally, one would have a reasonable expectation of success given that Davidson et al. teach inhibition of expression for a HD gene using a siRNA targeted to a HD nucleotide sequence and further one would have had a reasonable expectation of success at introducing chemical modifications wherein about 100% of the nucleotides were modified given that Rana specifically teach such siRNA are more stable and such siRNA are capable of eliciting RNA interference activity in cells. Further, one would have a reasonable expectation of success because chemical modifications of siRNA, adding stability and specificity to oligonucleotides were known in the art at the time of the invention was made.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention.

Response to Applicant's Arguments

Applicants argue there would have been no motivation to combine the teachings of Hayden et al. with the teaching of Hammond et al. because Hammond et al. merely teaches a generalized approach to RNAi and fails to consider HD as a potential target for RNAi. Applicant is reminded that Hammond et al. was applied under a 103 rejection based on a combination of references and not just the teachings of one reference.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a siRNA molecule, as taught by Hammond et al. to target a gene encoding HD, as taught by Hayden et al. Applicant argues that it would have only been obvious to try siRNA against HD and "obvious to try" is an improper standard for establishing obviousness. To the contrary, one of skill in the art would have been motivated to make a siRNA, given that Hammond et al. teach siRNA was known at the time to be more sequence specific and potent than antisense. Therefore, not only would one of skill in the art been clearly motivated to make a siRNA to HD, one of skill in the art would have had a reasonable expectation of success at interfering with expression from a target nucleic acid encoding a huntingtin protein.

Applicant argues Matulic-Adamic et al. is not pertinent to the problem addressed by the presently claimed compounds because Matulic-Adamic et al. is drawn to a ribozyme which is unrelated to RNAi. Matulic-Adamic et al. is relied upon to teach obvious chemical modifications to any nucleic acid molecule, such as a siRNA, for the purpose of increasing nuclease resistance, stability and target specificity: modifications that would be obvious to one of skill in the art to incorporate into a nucleic acid molecule used to target a specific gene for inhibition of expression.

Therefore, as discussed above, in the absence of evidence to the contrary, the invention, as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Kimberly Chong
Examiner Art Unit 1635

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PRIMARY EXAMINER